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Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

02007049.6

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

DEN HAAG, DEN
THE HAGUE,
LA HAYE, LE 10/03/03

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Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

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GERMANY

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SEE PAGE 1 OF THE DESCRIPTION FOR THE ORIGINAL TITLE.
THE APPLICANT'S NAME AT THE TIME OF FILING OF THE APPLICATION WAS: BYK GULD EN. THE TRANSFERT HAS TAKEN EFFECT FROM 12.07.02.

PATENT APPLICATION

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Novel Alkoxypyridine-Derivatives

Novel Alkoxypyridine-Derivatives

Field of application of the invention

The invention relates to novel alkoxy-pyridine derivatives, which are used in the pharmaceutical industry for the production of medicaments.

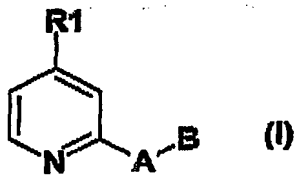
Known technical background

In the German Patent Application DE 2504252 and in the European Patent Application EP 0125766 3H-imidazo[4,5-b]pyridine derivatives with anti-ulcer activity are described.

Description of the invention

It has now been found that the alkoxy-pyridine derivatives, which are described in greater details below, have surprising and particularly advantageous properties.

The invention thus relates to compounds of formula I



(I)

in which

R1 is 1-4C-alkoxy,

A is 1-4C-alkylene,

B represents 3H-imidazo[4,5-b]pyridin-2-yl, 3H-imidazo[4,5-b]pyridin-2-yl substituted by R2 and/or R3, 9H-purin-8-yl or 9H-purin-8-yl substituted by R4 and/or R5, where

R2 is halogen, hydroxyl, nitro, amino, 1-7C-alkyl, trifluoromethyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy, mono- or di-1-4C-alkylaminocarbonyl, mono- or di-1-4C-alkylaminosulfonyl, 1-4C-alkylcarbonylamino, 1-4C-alkylsulfonylamino, phenyl, phenyl substituted by R21, phenyl-1-4C-alkyl, phenyl-1-4C-alkyl wherein the phenyl moiety is substituted by R22, phenyl-1-4C-alkoxy, pyridyl, pyridyl substituted by R23, pyridyl-1-4C-alkyl, pyridyl-1-4C-alkyl wherein the pyridyl moiety is substituted by R24, where

R21 is cyano, halogen, carboxyl, 1-4C-alkyl, 1-4C-alkoxy, aminocarbonyl, mono-or di-1-4C-alkylaminocarbonyl, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonyl, aminosulfonyl or mono-or di-1-4C-alkylaminosulfonyl,

R22 is halogen, 1-4C-alkyl or 1-4C-alkoxy,

R23 is halogen, 1-4C-alkyl or 1-4C-alkoxy,

R24 is halogen, 1-4C-alkyl or 1-4C-alkoxy,

R3 is halogen, 1-4C-alkyl or 1-4C-alkoxy,

R4 is halogen, amino, 1-4C-alkyl, 1-4C-alkoxy or phenyl,

R5 is halogen, 1-4C-alkyl or 1-4C-alkoxy,

the salts, the N-oxides and the salts of the N-oxides of these compounds.

1-4C-Alkyl is a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and methyl radicals.

1-7C-Alkyl is a straight-chain or branched alkyl radical having 1 to 7 carbon atoms. Examples are the heptyl, isoheptyl (5-methylhexyl), hexyl, isohexyl (4-methylpentyl), neohexyl (3,3-dimethylbutyl), pentyl, isopentyl (3-methylbutyl), neopentyl (2,2-dimethylpropyl), butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and methyl radicals.

1-4C-Alkylene is a straight chain alkylene radical having 1 to 4 carbon atoms. Examples which may be mentioned in this context are the methylene ($-CH_2-$), ethylene ($-CH_2-CH_2-$), trimethylene ($-CH_2-CH_2-CH_2-$) and the tetramethylene ($-CH_2-CH_2-CH_2-CH_2-$) radical.

1-4C-Alkoxy is a radical which, in addition to the oxygen atom, contains a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Alkoxy radicals having 1 to 4 carbon atoms which may be mentioned in this context are, for example, the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy, ethoxy and methoxy radicals.

3-7C-Cycloalkyl stands for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, of which cyclopropyl, cyclobutyl and cyclopentyl are preferred.

3-7C-Cycloalkyl-1-4C-alkyl stands for one of the abovementioned 1-4C-alkyl radicals, which is substituted by one of the abovementioned 3-7C-cycloalkyl radicals. Examples which may be mentioned are the cyclopropylmethyl, the cyclohexylmethyl and the cyclohexylethyl radicals.

Halogen within the meaning of the present invention is bromine, chlorine or fluorine.

1-4C-Alkoxy which is completely or predominantly substituted by fluorine is, for example, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-trifluoroethoxy and in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and the difluoromethoxy radical, of which the difluoromethoxy radical is preferred. "Predominantly" in this connection means that more than half of the hydrogen atoms of the 1-4C-alkoxy groups are replaced by fluorine atoms.

1-4C-Alkoxy-1-4C-alkoxy stands for one of the abovementioned 1-4C-alkoxy radicals which is substituted by the same or another of the abovementioned 1-4C-alkoxy radicals. Examples which may be mentioned are the 2-(methoxy)ethoxy ($-O-CH_2-CH_2-O-CH_3$) and the 2-(ethoxy)ethoxy radical ($-O-CH_2-CH_2-O-CH_2-CH_3$).

1-4C-Alkoxy-1-4C-alkyl stands for one of the abovementioned 1-4C-alkyl radicals which is substituted by one of the abovementioned 1-4C-alkoxy radicals. Examples which may be mentioned are the 2-ethoxyethyl and the 3-methoxypropyl radical.

Mono- or Di-1-4C-alkylamino radicals contain in addition to the nitrogen atom, one or two of the abovementioned 1-4C-alkyl radicals. Preferred are the di-1-4C-alkylamino radicals, especially the dimethylamino, the diethylamino and the diisopropylamino radical.

Mono- or Di-1-4C-alkylaminocarbonyl radicals contain in addition to the carbonyl group one of the abovementioned mono- or di-1-4C-alkylamino radicals. Examples which may be mentioned are the N-methyl- the N,N-dimethyl-, the N-ethyl-, the N-propyl-, the N,N-diethyl- and the N-isopropylaminocarbonyl radical.

Mono-or Di-1-4C-alkylaminosulfonyl stands for a sulfonyl group to which one of the abovementioned mono- or di-1-4C-alkylamino radicals is bonded. Examples which may be mentioned are the methylaminosulfonyl, the dimethylaminosulfonyl and the ethylaminosulfonyl radical.

An 1-4C-Alkylcarbonylamino radical is, for example, the propionylamino [$C_3H_7C(O)NH-$] and the acetylamino radical [$CH_3C(O)NH-$].

An 1-4C-Alkylsulfonylamino radical is, for example, the propylsulfonylamino [$C_3H_7S(O)_2NH-$] and the methylsulfonylamino radical [$CH_3S(O)_2NH-$].

1-4C-Alkoxycarbonyl is a carbonyl group to which one of the abovementioned 1-4C-alkoxy radicals is bonded. Examples are the methoxycarbonyl [$CH_3O-C(O)-$] and the ethoxycarbonyl [$CH_3CH_2O-C(O)-$] radical.

Phenyl-1-4C-alkoxy stands for one of the abovementioned 1-4C-alkoxy radicals, which is substituted by the phenyl radical. Examples which may be mentioned are the benzyloxy and the phenethoxy radical.

Phenyl-1-4C-alkyl stands for one of the abovementioned 1-4C-alkyl radicals, which is substituted by an phenyl radical. Examples which may be mentioned are the phenylethyl and the benzyl radical.

Pyridyl-1-4C-alkyl stands for one of the abovementioned 1-4C-alkyl radicals, which is substituted by an pyridyl radical. Examples which may be mentioned are the pyridylethyl and the pyridylmethyl radical.

N-oxide denotes the N-oxide on the pyridine which is substituted by R1.

3H-imidazo[4,5-b]pyridin-2-yl radicals substituted by R2 and/or R3 which may be mentioned are 7-methyl-3H-imidazo[4,5-b]pyridin-2-yl, 5,7-dimethyl-3H-imidazo[4,5-b]pyridin-2-yl, 5-methoxy-3H-imidazo[4,5-b]pyridin-2-yl, 6-brom-3H-imidazo[4,5-b]pyridin-2-yl, 7-methoxy-3H-imidazo[4,5-b]pyridin-2-yl, 7-hydroxy-3H-imidazo[4,5-b]pyridin-2-yl, 7-ethoxy-3H-imidazo[4,5-b]pyridin-2-yl, 7-methoxy-ethoxy-imidazo[4,5-b]pyridin-2-yl, 7-(1,1,1-trifluoroethoxy)-3H-imidazo[4,5-b]pyridin-2-yl, 7-(phenylethoxy)-3H-imidazo[4,5-b]pyridin-2-yl, 7-(phenylethyl)-3H-imidazo[4,5-b]pyridin-2-yl, 7-(tolylethyl)-3H-imidazo[4,5-b]pyridin-2-yl, 7-(pyrid-4-ylethyl)-3H-imidazo[4,5-b]pyridin-2-yl, 7-(pyrid-2-ylethyl)-3H-imidazo[4,5-b]pyridin-2-yl, 7-(pyrid-3-ylethyl)-3H-imidazo[4,5-b]pyridin-2-yl, 7-(4-methoxypyrid-2-ylethyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-phenyl-3H-imidazo[4,5-b]pyridin-2-yl, 6-n-butyl-3H-imidazo[4,5-b]pyridin-2-yl, 6-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(4-methylphenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-nitro-3H-imidazo[4,5-b]pyridin-2-yl, 6-(pyrid-3-yl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-(4-cyanophenyl)-3H-imidazo[4,5-b]pyridin-2-yl, 6-methyl-3H-imidazo[4,5-b]pyridin-2-yl and 6-trifluoromethyl-3H-imidazo[4,5-b]pyridin-2-yl.

9H-purin-8-yl radicals substituted by R4 and/or R5 which may be mentioned are 6-methoxy-9H-purin-8-yl, 6-ethoxy-9H-purin-8-yl, 2-methyl-9H-purin-8-yl, 2-ethyl-9H-purin-8-yl, 2-amino-9H-purin-8-yl, 2-chloro-9H-purin-8-yl and 2-phenyl-9H-purin-8-yl.

Suitable salts for compounds of the formula I - depending on substitution - are all acid addition salts or all salts with bases. Particular mention may be made of the pharmacologically tolerable inorganic and organic acids and bases customarily used in pharmacy. Those suitable are, on the one hand, water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulphuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulphosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulphonic acid, methanesulphonic acid or 3-hydroxy-2-naphthoic acid, the acids being

employed in salt preparation - depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

On the other hand, salts with bases are - depending on substitution - also suitable. As examples of salts with bases are mentioned the lithium, sodium, potassium, calcium, aluminium, magnesium, titanium, ammonium, meglumine or guanidinium salts, here, too, the bases being employed in salt preparation in an equimolar quantitative ratio or one differing therefrom.

Pharmacologically intolerable salts, which can be obtained, for example, as process products during the preparation of the compounds according to the invention on an industrial scale, are converted into pharmacologically tolerable salts by processes known to the person skilled in the art.

According to expert's knowledge the compounds of the invention as well as their salts may contain, e.g. when isolated in crystalline form, varying amounts of solvents. Included within the scope of the invention are therefore all solvates and in particular all hydrates of the compounds of formula I as well as all solvates and in particular all hydrates of the salts of the compounds of formula I.

Compounds of formula I to be emphasized are those in which

R1 is methoxy,

A is ethylene,

B represents 3H-imidazo[4,5-b]pyridin-2-yl, 3H-imidazo[4,5-b]pyridin-2-yl substituted by R2 and/or R3, 9H-purin-8-yl or 9H-purin-8-yl substituted by R4 and/or R5, where

R2 is halogen, nitro, 1-7C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy, phenyl, phenyl substituted by R21, phenyl-1-4C-alkyl, phenyl-1-4C-alkyl wherein the phenyl moiety is substituted by R22, phenyl-1-4C-alkoxy, pyridyl, pyridyl substituted by R23, pyridyl-1-4C-alkyl, pyridyl-1-4C-alkyl wherein the pyridyl moiety is substituted by R24, where
R21 is cyano, halogen, carboxyl, 1-4C-alkyl, 1-4C-alkoxy, aminocarbonyl, mono-or di-1-4C-alkylaminocarbonyl, 1-4C-alkylcarbonylamino or 1-4C-alkoxycarbonyl,
R22 is halogen, 1-4C-alkyl or 1-4C-alkoxy,
R23 is 1-4C-alkyl,
R24 is halogen, 1-4C-alkyl or 1-4C-alkoxy,

R3 is 1-4C-alkyl,

R4 is halogen, 1-4C-alkyl or 1-4C-alkoxy,

R5 is halogen or 1-4C-alkyl,

the salts, the N-oxides and the salts of the N-oxides of these compounds.

Compounds of formula I which are particularly to be emphasized are those in which

R1 is methoxy,

A is ethylene,

B is 3H-imidazo[4,5-b]pyridin-2-yl, 7-methyl-3H-imidazo[4,5-b]pyridin-2-yl, 5,7-dimethyl-3H-imidazo[4,5-b]pyridin-2-yl, 6-methoxy-3H-imidazo[4,5-b]pyridin-2-yl, 6-bromo-3H-imidazo[4,5-b]pyridin-2-yl or 9H-purin-8-yl,

the salts, the N-oxides and the salts of the N-oxides of these compounds.

A special embodiment of the compounds of the present invention include those compounds of formula I in which R1 is methoxy.

Another special embodiment of the compounds of the present invention include those compounds of formula I in which A is ethylene.

A further special embodiment of the compounds of the present invention include those compounds of formula I in which R1 is methoxy and A is ethylene.

Another further special embodiment of the compounds of the present invention include those compounds of formula I in which R1 is methoxy, A is ethylene and B represents 3H-imidazo[4,5-b]pyridin-2-yl or 3H-imidazo[4,5-b]pyridin-2-yl substituted by R2 and/or R3.

Still a further special embodiment of the compounds of the present invention include those compounds of formula I in which R1 is methoxy, A is ethylene and B represents 9H-purin-8-yl or 9H-purin-8-yl substituted by R4 and/or R5.

The compounds of formula I according to the invention can, for example, be prepared as described in reaction scheme 1. In reaction scheme 1 the synthesis of compounds of formula I in which R1 is 1-4C-alkoxy, A is ethylene and B is an unsubstituted or by R2 and/or R3 substituted 3H-imidazo[4,5-b]pyridin-2-yl radical is described.

In a first reaction step the nitro group of the commercially available 4-nitro-2-picoline-N-oxide is exchanged by an 1-4C-alkoxy group. The resulting 4-(1-4C)-alkoxy-2-picoline-N-oxide (compound of formula VIII) is then via a rearrangement and an oxidation step converted to 4-(1-4C)-alkoxy-pyridin-2-carbaldehyd (compound of formula VI).

The carbon chain in 2-position of the compounds of formula VI is lengthened, for example, by a condensation (with a malonic acid derivative) and a subsequent hydrogenation reaction. Alternatively, the carbon chain can be lengthened using a Wittig reaction followed by a hydrogenation reaction.

In the last step the methyl 3-(4-(1-4C)-alkoxypyridin-2-yl)propionate (compound of formula IV) or the corresponding acid (compound of formula III) are converted with a 2,3-diaminopyridine derivative (compounds of formula II) to give the compounds of formula I.

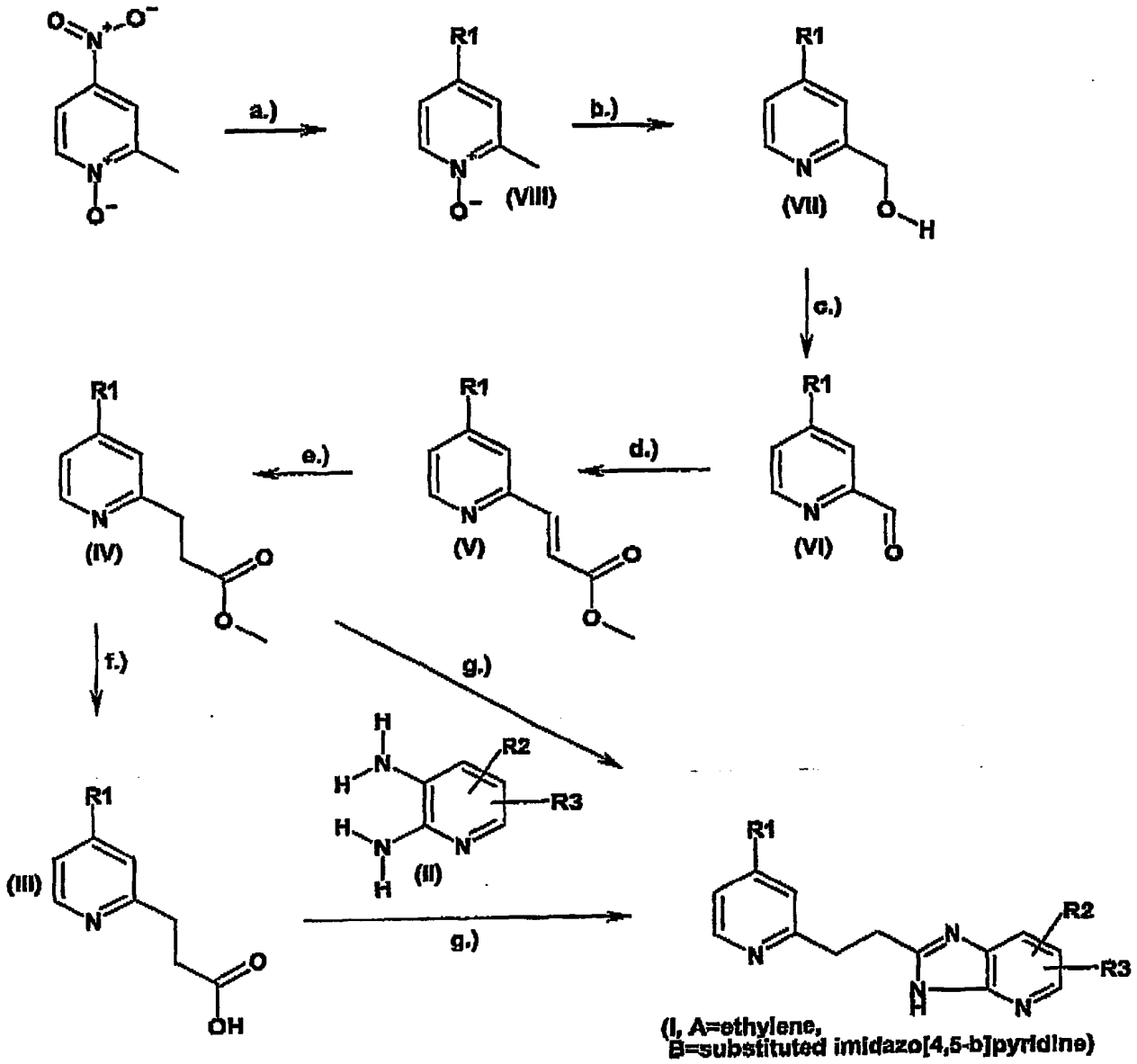
The synthesis of 4-methoxy-pyridin-2-carbaldehyde (compound of formula VI) is described for example in Ashimori et al, Chem Pharm Bull 38, 2446-2458 (1990).

The synthesis of 3-(4-methoxypyridin-2-yl)propionic acid (compound of formula III) is described in the paragraph Starting Compounds.

Compounds of formula II, in which R2 and R3 have the meanings indicated above are either known or can be prepared in a known manner.

Compounds of formula I, in which B represents an unsubstituted or by R4 and/or R5 substituted 9H-purin-8-yl radical instead of an unsubstituted or by R2 and/or R3 substituted 3H-imidazo[4,5-b]pyridin-2-yl radical can be prepared analoguously to the synthesis described in reaction scheme 1 using an 5,6-diaminopyrimidine derivative instead of the 2,3-diaminopyridine derivative.

Reaction Scheme 1:



a.) NaR1/R1H b.)1. Ac_2O 2. NaOH c.) 4-Methoxy-TEMPO/NaOCl

d.)Monoethyl malonate potassium salt/piperidine/pyridine

e.)H_2/Pd/C (10%) f.) NaOH g.) Polyphosphoric acid

The compounds of formula I can be converted, optionally, into their N-oxides, for example with the aid of hydrogen peroxide in methanol or with the aid of m-chloroperoxybenzoic acid in dichloromethane.

The person skilled in the art is familiar on the basis of his/her expert knowledge with the reaction conditions which are specifically necessary for carrying out the N-oxidation.

Suitably, the conversions are carried out analogous to methods which are familiar per se to the person skilled in the art, for example, in the manner which is described in the following examples.

It is known to the person skilled in the art that if there are a number of reactive centers on a starting or intermediate compound it may be necessary to block one or more reactive centers temporarily by protective groups in order to allow a reaction to proceed specifically at the desired reaction center. A detailed description for the use of a large number of proven protective groups is found, for example, in T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991.

The substances according to the invention are isolated and purified in a manner known per se, e.g. by distilling off the solvent in vacuo and recrystallizing the residue obtained from a suitable solvent or subjecting it to one of the customary purification methods, such as column chromatography on a suitable support material.

Salts are obtained by dissolving the free compound in a suitable solvent (for example a ketone like acetone, methylethylketone, or methylisobutylketone, an ether, like diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol, such as ethanol, isopropanol) which contains the desired acid, or to which the desired acid is then added. The salts are obtained by filtering, reprecipitating, precipitating with a non-solvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by basification into the free compounds which, in turn, can be converted into salts. In this manner, pharmacologically non-tolerable salts can be converted into pharmacologically tolerable salts.

The following examples illustrate the invention in greater detail, without restricting it. As well, further compounds of formula I, of which the preparation is explicitly not described, can be prepared in an analogous way or in a way which is known by a person skilled in the art using customary preparation methods.

The compounds, which are mentioned in the examples as well as their salts are preferred compounds of the invention.

Examples

Final products

1. **2-[2-(4-Methoxypyridin-2-yl)ethyl]-3H-imidazo[4,5-b]pyridine**

With stirring, a mixture of 0.643 g of methyl 3-(4-methoxypyridin-2-yl)propionate (starting material A2), 0.359 g of 2,3-diaminopyridine and 10 g of polyphosphoric acid (PPA) is heated at 160°C for 1 h. After cooling, the mixture is poured into about 50 ml of ice-water and then neutralized (pH 7-8) using 6N aqueous sodium hydroxide solution. The mixture is extracted three times with dichloromethane/methanol 9:1, the combined organic phases are evaporated to dryness and the residue is chromatographed on a silica gel column (dichloromethane/methanol 15:1). Concentration of the chromatographically pure fractions gives 0.36 g of an oil which crystallizes on standing. The product is recrystallized from ethyl acetate/ petroleum ether, giving 0.278 g of the title compound as a light-beige powder of m.p. 116-117°C; the mass spectrum shows the molecular peaks MH^+ and $2MNa^+$ at 255.3 and 530.9 Da.

2. **8-[2-(4-Methoxypyridin-2-yl)ethyl]-9H-purine**

Similarly to Example 1, 0.384 g of methyl 3-(4-methoxypyridin-2-yl)propionate (starting material A2), 0.216 g of 4,5-diaminopyrimidine and 4 g of PPA give, after 2 h at 140°C, 0.175 g of the title compound of m.p. 150-152°C (from ethyl acetate/petroleum ether). The mass spectrum shows the molecular peaks MH^+ and $2MNa^+$ at 256.3 and 532.8 Da.

3. **2-[2-(4-Methoxypyridin-2-yl)ethyl]-7-methyl-3H-imidazo[4,5-b]pyridine**

Similarly to Example 1, 0.766 g of methyl 3-(4-methoxypyridin-2-yl)propionate (starting material A2), 0.481 g of 2,3-diamino-4-methylpyridine and 8 g of PPA give, after dilution with ice-water and neutralization, a solid which is crystallized from ethyl acetate/ petroleum ether. This gives 0.495 g of the title compound of m.p. 143-144°C. The mass spectrum shows the molecular peaks MH^+ and $2MNa^+$ at 269.3 and 568.9 Da.

4. **2-[2-(4-Methoxypyridin-2-yl)ethyl]-5,7-dimethyl-3H-imidazo[4,5-b]pyridine**

Similarly to Example 3, 0.35 g of methyl 3-(4-methoxypyridin-2-yl)propionate (starting material A2), 0.245 g of 2,3-diamino-4,6-dimethylpyridine and 3.5 g of PPA give, after dilution with ice-water and neutralization, a solid which is crystallized from ethyl acetate/petroleum ether. This gives 0.335 g of the

title compound of m.p. 176-178°C. The mass spectrum shows the molecular peaks MH^+ and $2MNa^+$ at 283.3 and 587.0 Da.

5. 2-[2-(4-Methoxypyridin-2-yl)ethyl]-5-methoxy-3H-imidazo[4,5-b]pyridine

Similarly to Example 1, 0.316 g of methyl 3-(4-methoxypyridin-2-yl)propionate (starting material A2), 0.225 g of 2,3-diamino-6-methoxypyridine and 4 g of PPA give, after two hours at 140°C and chromatography using toluene/acetone 2:1, 0.103 g of the title compound of m.p. 93-95°C (from ethyl acetate/petroleum ether). The mass spectrum shows the molecular peaks MH^+, MNa^+ and $2MNa^+$ at 285.3, 307.2 and 591.0 Da.

6. 2-[2-(4-Methoxypyridin-2-yl)ethyl]-6-bromo-3H-imidazo[4,5-b]pyridine

Similarly to Example 1, 3.74 g of 3-(4-methoxypyridin-2-yl)propionic acid (starting material A1), 3.00 g of 2,3-diamino-5-bromopyridine and 120 g of PPA (24 hours at 140°C) give, after dilution with ice-water and neutralization, a solid which is crystallized from ethyl acetate/petroleum ether. This gives 3.48 g of the title compound of m.p. 207-209°C. The mass spectrum shows the molecular peak MH^+ at 335.1 Da.

Starting materials:

A1. 3-(4-Methoxypyridin-2-yl)propionic acid

41.95 g of methyl 3-(4-methoxypyridin-2-yl)propionate (starting material A2) are dissolved in 700 ml of tetrahydrofuran, and 217 ml of 1N sodium hydroxide solution are added. The mixture is stirred at RT until no more starting material is detectable (TLC). The mixture is neutralized using 217 ml of 1N hydrochloric acid solution, evaporated to dryness using a rotary evaporator and dried under high vacuum. The colorless residue is ground and extracted four times with dichloromethane/methanol (9:1). The combined extracts are evaporated to dryness. This gives 33.2 g of the title compound as a colorless powder of m.p. 131-132°C. The mass spectrum shows the molecular peak MH^+ at 182 Da.

A2. Methyl 3-(4-methoxypyridin-2-yl)propionate

43.1 g of methyl 3-(4-methoxypyridin-2-yl)acrylate (starting material A3) in 600 ml of methanol are hydrogenated over 3.0 g of Pd/C (10%) until the starting material has disappeared (TLC). The catalyst is filtered off, and the mixture is then concentrated and dried under high vacuum. This gives 41.95 g of the title compound as a light-yellow oil. The mass spectrum shows the molecular peak MH^+ at 196 Da.

A3. Methyl 3-(4-methoxypyridin-2-yl)acrylate

A mixture of 45 g of 4-methoxypyridine-2-carbaldehyde (Ashimori et al., Chem.Pharm.Bull. 38, 2446-2458 (1990)), 75.80 g of pyridine hydrochloride, 102.45 g of monomethyl malonate potassium salt and 4.1 ml of piperidine in 700 ml of pyridine are slowly heated, with stirring, to 120°C. When the evolution of gas starts, the heating source is temporarily removed to stop the reaction from becoming too violent. Once the reaction has subsided, the mixture is stirred at 120°C for a further 2.5 h, and the pyridine is then distilled off under reduced pressure. The residue is partitioned between ethyl acetate/water and the organic phase is washed with water and dried. The residue obtained after concentration is chromatographed on a silica gel column using ethyl acetate/petroleum ether 2:1. This initially gives 43.2 g of the title compound as a yellow oil which crystallizes on standing and then shows a m.p. of 80-82°C. The mass spectrum shows the molecular peak MH^+ at 194 Da.

Commercial applicability

The compounds according to the invention have valuable pharmacological properties which make them commercially utilizable. They are selective inhibitors of the enzyme inducible nitic oxide synthase. Nitric oxide synthases (NO-syntases, NOSs) are enzymes that generate NO and citrulline from the amino acid arginine. NO is long known as a signalling molecule in most living organisms including mammals and humans. The most prominent action of NO is it's smooth muscle relaxing activity, which is caused on the molecular level by the activation of soluble guanylate cyclase. In the last years a lot of other enzymes have been shown to be regulated by NO or reaction products of NO.

There exist three isoforms of NO-synthases which fall into two classes and differ in their physiologic functions and molecular properties. The first class, known as constitutive NO-synthases, comprises of the endothelial NO-synthase and the neuronal NO-synthase. Both isoenzymes are expressed constitutively in various cell types, but are most prominent in endothelial cells of blood vessel walls (therefore called endothelial NO-synthase, eNOS or NOS-III) and in neuronal cells (therefore called neuronal NO-synthase, nNOS or NOS-I). Activation of these two enzymes is dependent on Ca^{2+}/Calmodulin which is generated by transient increases of the intracellular free Ca^{2+} concentration. Activation of constitutive isoforms leads to transient bursts of nitric oxide resulting in nanomolar cellular or tissue NO concentrations. The endothelial isoform is involved in the physiologic regulation of blood pressure. NO generated by the neuronal isoform seems to have neurotransmitter function and the neuronal isoform is among other regulatory processes involved in memory function (long term potentiation).

In contrast to the constitutive isoforms the activation of inducible NO-synthase (iNOS, NOS-II), the sole member of the second class, is performed by transcriptional activation of the iNOS-promoter. Proinflammatory stimuli lead to transcription of the gene for inducible NO-synthase, which is catalytically active without increases in the intracellular Ca^{2+}-concentration. Due to the long half live of the inducible NO-synthase and the unregulated activity of the enzyme, high micromolar concentrations of NO are generated over longer time periods. These high NO-concentrations alone or in cooperation with other reactive radicals such as O_2^- are cytotoxic. Therefore, in situations of microbial infections, iNOS is involved in cell killing by macrophages and other immune cells during early nonspecific immune responses.

There are a number of pathophysiological situations which among others are characterized by the high expression of inducible NO-synthase and concomittant high NO concentrations. It has been shown that these high NO concentrations alone or in combination with other radical species lead to tissue and organ damage and are causally involved in these pathophysiologies. As inflammation is characterized by the expression of proinflammatory enzymes, including inducible NO-synthase, acute and chronical inflammatory processes are promissing diseases for the therapeutic application of selective inhibitors of

inducible NO-synthase. Other pathophysiologies with by high NO-production from inducible NO-synthase are several forms of shock (septic, hemorrhagic and cytokine-induced).
It is clear that nonselective NO-synthase inhibitors will lead to cardiovascular and neuronal side effects due to concomitant inhibition of constituitve NO-synthase isoforms.

It has been shown in in-vivo animal models of septic shock that reduction of circulating plasma NO-levels by NO-scavenger or inhibition of inducible NO-synthase restores systemic blood pressure, reduces organ damage and increases survival (deAngelo Exp. Opin. Pharmacother. 19-29, 1999; Redl et al. Shock 8, Suppl. 51, 1997; Strand et al. Crit.Care Med. 26, 1490-1499, 1998). It has also been shown that increased NO production during septic shock contributes to cardiac depression and myocardial dysfunction (Sun et al. J. Mol.Cell Cardiol. 30, 989-997, 1998). Furthermore there are also reports showing reduced infarct size after occlusion of the left anterior coronary artery in the presence of NO-synthase inhibitors (Wang et al. Am. J. Hypertens. 12, 174-182, 1999). Considerable inducible NO-synthase activity is found in human cardiomyopathy and myocarditis, supporting the hypothesis that NO accounts at least in part for the dilatation and impaired contractility in these pathophysiologies (de Belder et al. Br. Heart. J. 4, 426-430, 1995).

In animal models of acute or chronic inflammation, blockade of inducible NO-synthase by isoform-selective or nonselective inhibitors or genetic knock out improves therapeutic outcome. It is reported that experimental arthritis (Connor et al. Eur. J. Pharmacol. 273, 15-24, 1995) and osteoarthritis (Pelletier et al. Arthritis & Rheum. 41, 1275-1286, 1998), experimental inflammations of the gastro-intestinal tract (Zingarelli et al. Gut 45, 199-209, 1999), experimental glomerulonephritis (Narita et al. Lab. Invest. 72, 17-24, 1995), experimental diabetes (Corbett et al. PNAS 90, 8992-8995, 1993), LPS-induced experimental lung injury is reduced by inhibition of inducible NO-synthase or in iNOS-knock out mice (Kristof et al. Am. J. Crit. Care. Med. 158, 1883-1889, 1998). A pathophysiological role of inducible NO-synthase derived NO is also discussed in chronic inflammatory diseases such as asthma, bronchitis and COPD.

Furthermore, in models of neurodegenerative diseases of the CNS such as MPTP-induced parkinsonism, amyloid peptide induced Alzheimer's disease (Ishii et al., FASEB J. 14, 1485-1489, 2000), malonate induced Huntington's disease (Connop et al. Neuropharmacol. 35, 459-465, 1996), experimental menengitis (Korytko & Boje Neuropharmacol. 35, 231-237, 1996) and experimental encephalitis (Parkinson et al. J. Mol. Med. 75, 174-186, 1997) a causal participation of NO and inducible NO-synthase has been shown.

Increased iNOS expression has been found in the brains of AIDS victims and it is reasonable to assume a role of iNOS in AIDS related dementia (Bagasra et al. J. Neurovirol. 3 153-167, 1997).

Other studies implicated nitric oxide as a potential mediater of microglia dependent primary demyelination a hallmark of multiple sklerosis (Parkinson et al. J. Mol. Med. 75, 174-186, 1997).

An inflammatory reaction with concomitant expression of inducible NO-synthase also takes place during cerebral ischemia and reperfusion (Iadecola et al. Stroke 27, 1373-1380, 1996). Resulting NO together with O_2^- from infiltrating neutrophils is thought to be responsible for cellular and organ damage. Also, in models of traumatic brain injury (Mesenge et al. J. Neurotrauma 13, 209-214, 1996; Wada et al. Neurosurgery 43, 1427-1436, 1998) NO-synthase inhibitors have been show to posses protective properties. A regulatory role for inducible NO-synthase has been reported in various tumor cell lines (Tozer & Everett Clin Oncol. 9. 357-264, 1997).

On account of their inducible NO-synthase-inhibiting properties, the compounds according to the invention can be employed in human and veterinary medicine and therapeutics, where an excess of nitric oxide due to increases in the activity of inducible NO-synthase is involved. They can be used without limitation for the treatment and prophylaxis of the following diseases:

Acute inflammatory diseases: Sepsic shock, sepsis, SIRS, hemorrhagic shock, shock states induced by cytokine therapy (IL-2, TNF), organ transplantation and transplant rejection, head trauma, acute lung injury, ARDS, inflammatory skin conditions such as sunburn, inflammatory eye conditions such as uveitis, glaucoma and conjunctivitis.

Chronic inflammatory diseases of peripheral organs and the CNS: gastrointestinal inflammatory diseases such as Crohn's disease, inflammatory bowel disease, ulcerative colitis, lung inflammatory diseases such as asthma and COPD, arthritic disorders such as rheumatoid arthritis, osteoarthritis and gouty arthritis, heart disorders such as cardiomyopathy and myocarditis, artherosklerosis, neurogenic inflammation, skin diseases such as psoriasis, dermatitis and eczema, diabetes, glomerulonephritis; dementias such as dementias of the Alzheimer's type, vascular dementia, dementia due to a general medical condition, such as AIDS-, Parkinson's disease, Huntington's induced dementias, ALS, multiple sklerosis; necrotizing vasculitides such as polyarteritis nodosa, serum sickness, Wegener's granulomatosis, Kawasaki's syndrom; headaches such as migraine, chronic tension headaches, cluster and vascular headaches, post-traumatic stress disorders; pain disorders such as neuropathic pain; myocardial and cerebral ischemia/reperfusion injury.

The compounds may also be useful in the treatment of cancers that express nitric oxide synthase.

The invention further relates to a method for the treatment of mammals, including humans, which are suffering from one of the abovementioned illnesses. The method is characterized in that a therapeuti-

cally active and pharmacologically effective and tolerable amount of one or more of the compounds according to the invention is administered to the ill mammal.

The invention further relates to the compounds according to the invention for use in the treatment and/or prophylaxis of illnesses, especially the illnesses mentioned.

The invention also relates to the use of the compounds according to the invention for the production of medicaments which are employed for the treatment and/or prophylaxis of the illnesses mentioned.

The invention furthermore relates to medicaments for the treatment and/or prophylaxis of the illnesses mentioned, which contain one or more of the compounds according to the invention.

The medicaments are prepared by processes which are known per se and familiar to the person skilled in the art. As medicaments, the compounds according to the invention (= active compounds) are either employed as such, or preferably in combination with suitable pharmaceutical auxiliaries and/or excipients, e.g. in the form of tablets, coated tablets, capsules, caplets, suppositories, patches (e.g. as TTS), emulsions, suspensions, gels or solutions, the active compound content advantageously being between 0.1 and 95% and where, by the appropriate choice of the auxiliaries and/or excipients, a pharmaceutical administration form (e.g. a delayed release form or an enteric form) exactly suited to the active compound and/or to the desired onset of action can be achieved.

The person skilled in the art is familiar with auxiliaries or excipients which are suitable for the desired pharmaceutical formulations on account of his/her expert knowledge. In addition to solvents, gel formers, ointment bases and other active compound excipients, for example antioxidants, dispersants, emulsifiers, preservatives, solubilizers, colorants, complexing agents or permeation promoters, can be used.

The administration of the medicaments according to the invention may be performed in any of the generally accepted modes of administration available in the art. Illustrative examples of suitable modes of administration include intravenous, oral, nasal, parenteral, topical, transdermal and rectal delivery. Oral and intravenous delivery are preferred.

For the treatment of disorders of the respiratory tract, the compounds according to the invention are preferably also administered by inhalation in the form of an aerosol; the aerosol particles of solid, liquid or mixed composition preferably having a diameter of 0.5 to 10 µm, advantagously of 2 to 6 µm.

Aerosol generation can be carried out, for example, by pressure-driven jet atomizers or ultrasonic atomizers, but advantageously by propellant-driven metered aerosols or propellant-free administration of micronized active compounds from inhalation capsules.

Depending on the inhaler system used, in addition to the active compounds the administration forms additionally contain the required excipients, such as, for example, propellants (e.g. Frigen in the case of metered aerosols), surface-active substances, emulsifiers, stabilizers, preservatives, flavorings, fillers (e.g. lactose in the case of powder inhalers) or, if appropriate, further active compounds.

For the purposes of inhalation, a large number of apparatuses are available with which aerosols of optimum particle size can be generated and administered, using an inhalation technique which is as right as possible for the patient. In addition to the use of adaptors (spacers, expanders) and pear-shaped containers (e.g. Nebulator®, Volumatic®), and automatic devices emitting a puffer spray (Autohaler®), for metered aerosols, in particular in the case of powder inhalers, a number of technical solutions are available (e.g. Diskhaler®, Rotadisk®, Turbohaler® or the inhaler described in European Patent Application EP 0 505 321), using which an optimal administration of active compound can be achieved.

For the treatment of dermatoses, the compounds according to the invention are in particular administered in the form of those medicaments which are suitable for topical application. For the production of the medicaments, the compounds according to the invention (= active compounds) are preferably mixed with suitable pharmaceutical auxiliaries and further processed to give suitable pharmaceutical formulations. Suitable pharmaceutical formulations are, for example, powders, emulsions, suspensions, sprays, oils, ointments, fatty ointments, creams, pastes, gels or solutions.

The medicaments according to the invention are prepared by processes known per se. The dosage of the active compounds is carried out in the order of magnitude customary for iNOS inhibitors. Topical application forms (such as ointments) for the treatment of dermatoses thus contain the active compounds in a concentration of, for example, 0.1-99%. The dose for administration by inhalation is customarily between 0.1 and 10 mg per day. The customary dose in the case of systemic therapy (p.o.) is between 0.3 and 30 mg/kg per day, (i. v.) is between 0.3 and 30 mg/kg/h.

Biological investigations

Measurement of inducible NO-synthase activity

The assay is performed in 96-well microtiter F-plates (Greiner, Frickenhausen, FRG) in a total volume of 100 µl in the presence of 100 nM calmodulin, 226 µM $CaCl_2$, 477 µM $MgCl_2$, 5 µM flavin-adenine-dinucleotide (FAD), 5 µM flavin mononucleotide (FMN), 0.1 mM NADPH, 7 mM glutathione, 10 µM BH4 and 100 mM HEPES pH 7.2. Arginine concentrations are 0.1 µM for enzyme inhibition experiments. 150000 dpm of [^{3}H]arginine are added to the assay mixture. Enzyme reaction is started by the addition of 4 µg of a crude cytosolic fraction containing human inducible NO-synthase and the reaction mixture is incubated for 45 to 60 min at 37°C. Enzyme reaction is stopped by adding 10 µl of 2M MES-buffer pH 5,0, 50 µl of the incubation mixture are transferred into a MADP N65 filtration microtiter plate (Millipore, Eschborn, FRG) containing already 50 µl of AG-50W-X8 cation exchange resin (Biorad, München, FRG). The resin in the Na loaded form is pre-equilibrated in water and 70 µl (corresponding to 50 µl dry beads) are pipetted under heavy stirring with a 8 channel pipette into the filtration plate. After pipetting 50 µl of the enzyme reaction mixture onto the filtration plates, the plates are placed on a filtration manifold (Porvair, Shepperton, UK) and the flow through is collected in Pico scintillation plates (Packard, Meriden, CT). The resin in the filtration plates is washed with 75 µl of water (1x50 µl and 1x 25 µl) which is also collected in the same plate as the sample. The total flow through of 125 µl is mixed with 175 µl of Microscint-40 scintillation cocktail (Packard) and the scintillation plate is sealed with TopSeal P-foil (Packard). Scintillation plates are counted in a szintillation counter.

For the measurement of inducible NO-synthase-inhibiting potencies of compounds increasing concentrations of inhibitors were included into the incubation mixture. IC_{50}-values were calculated from the percent inhibition at given concentrations by nonlinear least-square-fitting.

The inhibitory values determined for the compounds according to the invention follow from the following table A, in which the compound numbers correspond to the example numbers.

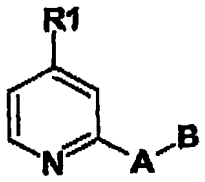
Table A

Inhibition of iNOS activity [measured as -logIC_{50} (mol/l)]

compound	-logIC_{50}
1	7.03
2	6.22
3	6.75
4	5.64
5	6.32
6	6.73

Patent claims

1. Compounds of formula I



(I)

in which

R1 is 1-4C-alkoxy,

A is 1-4C-alkylene,

B represents 3H-imidazo[4,5-b]pyridin-2-yl, 3H-imidazo[4,5-b]pyridin-2-yl substituted by R2 and/or R3, 9H-purin-8-yl or 9H-purin-8-yl substituted by R4 and/or R5, where

R2 is halogen, hydroxyl, nitro, amino, 1-7C-alkyl, trifluoromethyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy, mono- or di-1-4C-alkylaminocarbonyl, mono- or di-1-4C-alkylaminosulfonyl, 1-4C-alkylcarbonylamino, 1-4C-alkylsulfonylamino, phenyl, phenyl substituted by R21, phenyl-1-4C-alkyl, phenyl-1-4C-alkyl wherein the phenyl moiety is substituted by R22, phenyl-1-4C-alkoxy, pyridyl, pyridyl substituted by R23, pyridyl-1-4C-alkyl, pyridyl-1-4C-alkyl wherein the pyridyl moiety is substituted by R24, where
R21 is cyano, halogen, carboxyl, 1-4C-alkyl, 1-4C-alkoxy, aminocarbonyl, mono-or di-1-4C-alkylaminocarbonyl, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonyl, aminosulfonyl or mono-or di-1-4C-alkylaminosulfonyl,
R22 is halogen, 1-4C-alkyl or 1-4C-alkoxy,
R23 is halogen, 1-4C-alkyl or 1-4C-alkoxy,
R24 is halogen, 1-4C-alkyl or 1-4C-alkoxy,

R3 is halogen, 1-4C-alkyl or 1-4C-alkoxy,

R4 is halogen, amino, 1-4C-alkyl, 1-4C-alkoxy or phenyl,

R5 is halogen, 1-4C-alkyl or 1-4C-alkoxy,

the salts, the N-oxides and the salts of the N-oxides of these compounds.

2. Compounds of formula I according to claim 1 in which

R1 is methoxy,

A is ethylene,

B represents 3H-imidazo[4,5-b]pyridin-2-yl, 3H-imidazo[4,5-b]pyridin-2-yl substituted by R2 and/or R3, 9H-purin-8-yl or 9H-purin-8-yl substituted by R4 and/or R5, where

R2 is halogen, nitro, 1-7C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy, phenyl, phenyl substituted by R21, phenyl-1-4C-alkyl, phenyl-1-4C-alkyl wherein the phenyl moiety is substituted by R22, phenyl-1-4C-alkoxy, pyridyl, pyridyl substituted by R23, pyridyl-1-4C-alkyl, pyridyl-1-4C-alkyl wherein the pyridyl moiety is substituted by R24, where
R21 is cyano, halogen, carboxyl, 1-4C-alkyl, 1-4C-alkoxy, aminocarbonyl, mono-or di-1-4C-alkylaminocarbonyl, 1-4C-alkylcarbonylamino or 1-4C-alkoxycarbonyl,
R22 is halogen, 1-4C-alkyl or 1-4C-alkoxy,
R23 is 1-4C-alkyl,
R24 is halogen, 1-4C-alkyl or 1-4C-alkoxy,

R3 is 1-4C-alkyl,

R4 is halogen, 1-4C-alkyl or 1-4C-alkoxy,

R5 is halogen or 1-4C-alkyl,

the salts, the N-oxides and the salts of the N-oxides of these compounds.

3. Compounds of formula I according to claim 1 in which

R1 is methoxy,

A is ethylene,

B is 3H-imidazo[4,5-b]pyridin-2-yl, 7-methyl-3H-imidazo[4,5-b]pyridin-2-yl, 5,7-dimethyl-3H-imidazo[4,5-b]pyridin-2-yl, 5-methoxy-3H-imidazo[4,5-b]pyridin-2-yl, 6-bromo-3H-imidazo[4,5-b]pyridin-2-yl or 9H-purin-8-yl,

the salts, the N-oxides and the salts of the N-oxides of these compounds.

4. Compounds of formula I according to one of the claims 1 or 2 in which R1 is methoxy and A is methylene.

5. Compounds of formula I according to one of the claims 1 or 2 in which R1 is methoxy, A is ethylene and B represents 3H-imidazo[4,5-b]pyridin-2-yl or 3H-imidazo[4,5-b]pyridin-2-yl substituted by R2 and/or R3.

6. Compounds of formula I according to one of the claims 1 or 2 in which R1 is methoxy, A is ethylene and B represents 9H-purin-8-yl or 9H-purin-8-yl substituted by R4 and/or R5.

7. Compounds of formula I according to claim 1 for the treatment of diseases.

8. Medicaments containing one or more compounds of formula I according to claim 1 together with the usual pharmaceutical auxiliaries and/or excipients.

9. Use of compounds of formula I according to claim 1 for the production of medicaments for the treatment of acute inflammatory diseases.

10. Use of compounds of formula I according to claim 1 for the production of medicaments for the treatment of chronic inflammatory diseases of peripheral organs and the CNS.

Abstract

The compounds of formula I in which R1, A and B the meanings as given in the description are novel effective iNOS inhibitors.